Emergency contraception: a review of current oral options

see also p 152

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Unintended pregnancy is a major public health concern in the United States. Every year about 3.5 million unintended pregnancies occur in this country, half of which result from contraceptive failure or inadequate contraceptive technique.[1] The use of emergency contraception (EC) in these women can reduce the number of unintended pregnancies and consequential abortions substantially. It has been estimated that three quarters of these situations could be avoided with the use of EC.[2]

The method described by Yuzpe a quarter century ago consists of two doses of ethinyl estradiol (100 µg) plus levonorgestrel (0.5 mg) spaced 12 hours apart. An alternative option is two doses of ethinyl estradiol (100 µg) plus norgestrel (1 mg), spaced 12 hours apart. The Food and Drug Administration (FDA) has approved the use of several oral contraceptives as part of the Yuzpe regimen for EC. Despite FDA approval, the manufacturers have declined to submit a new drug application for this indication (table 1).[3,4] Even though several different methods of EC are available, this review addresses only oral EC medications that have an FDA-labeled indication for EC.

Summary points

- Emergency contraception (EC) should be undertaken within 72 hours of unprotected sexual intercourse; the sooner it is started, the more effective it will be in preventing pregnancy (recent data indicate that EC is effective <120 hours)
- EC should not be used as a regular form of birth control
- EC does not cause an abortion
- If a woman is pregnant or becomes pregnant when she takes EC, it will not harm the fetus
- Common adverse effects of EC include nausea, emesis, headache, irregular bleeding, breast tenderness, and abdominal cramping
- An antiemetic can be prescribed to prevent nausea and emesis
- If emesis occurs within 1 hour after a dose, the dose should be repeated
- At this time, a prescription is needed to obtain EC in the United States, but pharmacists in Washington and California have collaborative prescribing privileges that allow them to evaluate patients and provide EC as indicated

DEFINITION

Emergency contraception refers to any device or drug that is used as an emergency procedure to prevent pregnancy after unprotected sexual intercourse.[5,6] Synonymous terms for EC include "the morning-after pill," postcoital contraception, interception, postovulatory contraception, "visiting pill," and "vacation pill." These terms are often misinterpreted as indicating abortion or are inappropriately associated with the abortifacient mifepristone (RU-486). An abortifacient is any device or drug that acts after implantation has occurred.[5] Once a blastocyst has implanted in the endometrium, it is defined as the beginning of pregnancy.[7] EC is not effective once implantation has taken place. Because it will not terminate an existing pregnancy, it is, therefore, not an abortifacient.

INDICATION

Emergency contraception is indicated for the prevention of pregnancy in women after a known or possible contraceptive failure or unprotected sexual intercourse and for victims of sexual assault. It is not recommended as a form of routine contraception. Although EC reduces the risk of pregnancy, it is much less effective than the regular use of standard contraception.[8,9]

THERAPEUTIC OPTIONS

Currently two oral EC products are commercially available in the United States, one a combination of ethinyl estradiol and levonorgestrel (Preven) and one that is levonorgestrel only (Plan B) (table 1). Both products require a prescription; however, patient access has been facilitated through various protocols, including the Emergency Contraception Hotline (1-888-NOT-2-Late [668-2528]) and the Emergency Contraception web site (ec.princeton.edu). These resources provide information about EC products and local participating providers. The web site also provides patient pamphlets in various foreign languages.

Each tablet of Preven contains levonorgestrel, 0.25 mg, and ethinyl estradiol, 0.05 mg. It is available in two different packages—as four EC tablets or as an EC kit, which includes a pregnancy test and a detailed patient information book. Each Plan B package comprises two tablets, each containing 0.75 mg of levonorgestrel.

Mechanism of action

Although the precise mechanism of action of either of these products has not been fully elucidated, both work in a similar manner. Several mechanisms have been postulated, depending on when during the menstrual cycle an exposure occurs. They are thought to act primarily by inhibiting or disrupting ovulation. In addition, they may act by interfering with tubal transport of the ova and/or

Table 1 *Available oral emergency contraceptives*

Commercially available EC*	Estrogen, µg	Progestin, mg	Tablets per dose, no. (color)†	Average wholesale price $‡
Oral EC products				
Ethinyl estradiol-levonorgestrel	50	0.25	2	19.94
Levonorgestrel (Plan B)		0.75	1	21.95
FDA-approved EC drugs§				
Alesse/Levlite	20	0.1	5 (pink)	32.95/32.62
Levlen/Nordette	30	0.15	4 (pale orange)	31.93
Trievlen/Triphasic	30	0.125	4 (yellow)	24.52
Norgestrel				
Lo/Ovral	30	0.3	4 (white)	34.04
Ovral	50	0.05	2 (white)	50.10
Ovrette		0.075	20 (yellow)	33.62

FDA = Food and Drug Administration.
*Trade names are given for information only and are not to be construed as endorsement by either the author or the editors of this journal.
†Oral hormonal EC consists of two doses. The first dose should be taken within 72 hours after unprotected intercourse, followed by a second dose 12 hours later.
‡Price of an intact oral contraceptive package, as some pharmacies may not break up the individual package (Facts and Comparisons Price Alert, Indianapolis, IN: January 2002).
§The manufacturers of these oral contraceptives, Berlex and Wyeth-Ayerst, have declined to submit new drug applications for their products to include EC; therefore, the package labeling does not include it.

sperm, thereby inhibiting fertilization, or by inhibiting implantation through alteration of the endometrium.[10,11]

Adverse effects

Both EC products have comparable adverse effects, the most commonly reported being nausea, emesis, abdominal pain, headache, menstrual irregularities, fatigue, dizziness, and breast tenderness. The incidence of nausea, emesis, and fatigue, however, is substantially less with levonorgestrel alone (Plan B).[12,13] Because of the short duration of treatment, long-term adverse effects are extremely unlikely. The use of EC is generally not associated with any serious adverse effects, even though the doses used are higher than those used for routine contraception. Compared with oral contraceptives, EC treatment is not associated with a substantially increased risk for venous thromboembolism.[14] For women at risk for venous thromboembolism, a history of thromboembolic disease, or stroke, levonorgestrel alone may be preferred because evidence is lacking that progestins may have procoagulant effects.

Efficacy

Although both agents are effective in reducing the expected number of pregnancies, comparative trials have shown that levonorgestrel alone (Plan B) is more efficacious in preventing pregnancy.[12,13] The use of the ethinyl estradiol-levonorgestrel combination prevents about 74% of pregnancies, whereas the use of levonorgestrel alone prevents about 85% of pregnancies when administered within 72 hours.[15] Factors affecting the efficacy of EC include treatment regimen compliance and time from failed contraception—known or suspected contraceptive failure or unprotected intercourse—to treatment. Even though the manufacturers recommend that treatment be initiated within 72 hours of unprotected intercourse, there is evidence that EC treatment is 72% to 85% effective when initiated between 72 and 120 hours after unprotected intercourse.[16] Therefore, women seeking treatment after 72 hours, but within 120 hours, should not be denied treatment if other alternatives are unacceptable. Nevertheless, treatment should be administered as soon as possible after failed contraception because the rate of pregnancy increases the longer treatment is delayed from the time of failed contraception.[17]

Drug interactions

Interactions known to occur with combined oral contraceptives and progestin-only contraceptive drugs may occur with the use of EC. The most common clinically encountered interactions with oral contraceptives, which have been shown to reduce their effectiveness, involve the use of antibiotics and anticonvulsants.[18,19] With the increased use of nonprescription medications and polypharmacy, prescribers should be aware of possible pharmacodynamic and pharmacokinetic interactions between EC and other medication (table 2).

Contraindications and warnings

Emergency contraception is relatively safe, with essentially no contraindications except pregnancy. It is not known whether the same contraindications for combined oral

Table 2 *Possible interactions with oral contraceptive (OC) medication*

Agents (trade name) that decrease effectiveness of OCs*	Agents (trade name) whose effectiveness is decreased by OCs*	Agents (trade name) whose effect is increased by OCs*
Barbiturates	Lorazepam (Ativan)	Alprazolam (Xanax)
Carbamazepine	Oxazepam	Ascorbic acid (vitamin C)
Ethosuximide (Zarontin)	Temazepam (Restoril)	Beta blockers
Griseofulvin	Warfarin (Coumadin)	Caffeine
Metronidazole		Corticosteroids
Nelfinavir mesylate (Viracept)		Cyclosporine
Oxcarbazepine (Trileptal)		Diazepam
Penicillins		Selegiline hydrochloride
Phenytoin (Dilantin)		Theophylline
Primidone		Triazolam (Halcion)
Rifamycins		Tricyclic antidepressants
Ritonavir (Norvir)		Warfarin (Coumadin)
St. John's wort†		
Tetracyclines		

*Trade names are given for information only and are not to be construed as endorsement by either the author or the editors of this journal. Where several formulations are available, a trade name has not been given.
†May cause breakthrough bleeding, but has not been reported to result in unexpected pregnancy.

contraceptives and progestin-only contraceptive drugs apply to the EC products; therefore, caution should be taken in patients using either of them (see Box). The same precautions taken with combined oral contraceptive and progestin-only contraceptive drugs should be considered with Preven and Plan B, respectively.

Contraindications to oral contraceptive drugs

Combined oral contraceptives (Preven)

- Known or suspected pregnancy
- Pulmonary embolism
- Ischemic heart disease
- History of cerebrovascular accident
- Valvular heart disease with complications
- Severe uncontrolled hypertension
- Diabetes with vascular involvement
- Headaches with focal neurologic symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Active liver tumors (benign and malignant) or liver disease
- Known hypersensitivity to any component of the product

Progestin-only contraceptives (Plan B)

- Known or suspected pregnancy
- Hypersensitivity to any component of the product
- Undiagnosed abnormal genital bleeding

Pregnancy is a contraindication to EC because EC is ineffective if a woman is pregnant. There is no significant increase of teratogenic risk on fetal development associated with the long-term use of oral contraceptives administered before pregnancy or taken inadvertently during early pregnancy.[20,21] Nonetheless, no studies have been conducted regarding the teratogenic effects associated with the use of EC. Health care professionals, however, should be alert to the possibility of ectopic gestation in women who become pregnant or who have lower abdominal pain after taking EC because it does not prevent extrauterine pregnancies.[22]

Dosage and administration

The first dose of either EC product (table 1) should be taken within 72 hours after failed contraception, followed by a second dose 12 hours after the first dose. Although a second dose at 12 hours is preferred, up to 16 hours should be reasonably effective. According to the product labeling, women using the Preven EC kit should use the supplied pregnancy test to identify an existing pregnancy. If a positive result is obtained, EC should not be administered. The pregnancy test could be saved to check for a pregnancy if menses do not occur in 21 days.

Should emesis occur within 1 hour after taking either dose, a replacement dose should be given. There are no set guidelines as to when a dose should be repeated. It seems reasonable to assume that if gastrointestinal symptoms are EC-mediated due to an effect on the central nervous system, absorption of the dose should have occurred before emesis.[23] Providing patients with a refill on the EC prescription would not be unreasonable if a woman has a history of frequent drug-induced nausea or emesis or contact with the prescriber is limited. To prevent emesis and the need to give a replacement dose, meclizine hydrochloride or an antiemetic could be prescribed. Meclizine, an antihistamine with antiemetic properties, is the only nonprescription antiemetic available in the United States. One dose of meclizine, 50 mg, 1 hour before the first dose of EC has been shown to significantly reduce nausea and emesis associated with use of EC.[24] If an antiemetic drug is prescribed, the patient should be instructed to take it 1 hour before each EC dose, depending on the specific agent's duration of action.

Health care practitioners should counsel patients on the correct use of EC, possible adverse effects, effective contraceptive methods, the risk for sexually transmissible diseases, safer sex practice, and the possibility of treatment failure. Patients should be advised to seek medical attention if menses have not begun within 3 weeks after EC treatment for the evaluation of pregnancy. Each patient should have some type of follow-up care, even if by telephone.

In Washington State, pharmacists working within a collaborative protocol with a physician are able to provide

Reproductive Health Technologies Project

Emergency contraception effectively reduces the risk of pregnancy after contraceptive failure

EC treatment to the community. This has both increased access to EC and reduced unwanted pregnancy rates in the state.[25] Effective January 1, 2002, pharmacists in California have been able to provide the same services. In addition, the manufacturers of both Preven and Plan B are applying for nonprescription status.

CONCLUSION

Although EC is not intended for routine contraceptive use, its use after failed contraception could minimize the number of unanticipated pregnancies, preventing the physical and emotional burden of an unwanted pregnancy, in addition to reducing health care costs. The use of EC, however, is limited by the lack of patient and practitioner awareness and treatment accessibility. Despite the primarily positive attitudes toward EC, patients and practitioner lack detailed knowledge of EC. For example, the misnomer morning-after pill gives the false perception that EC treatment must be initiated immediately after failed contraception. Furthermore, medical consultation after failed contraception may be challenging to arrange and embarrassing for women requesting EC. A movement is growing to make EC available without a prescription and to promote public awareness, in the hope of increasing patient accessibility.

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